and Dr. Himwich have considerable information on immunological problems in their physiological notebooks. We hope very much that they will publish accounts of what they have observed.

In view of numerous uncertainties and with the realization that a bacteriologist can not speak with any authority on intricate clinical and physiological questions, I must state my conclusions in somewhat negative terms. In my opinion, (1) the concentration of sugar in the blood of diabetics has little or nothing to do with their states of resistance or susceptibility to infection; (2) such factors as loss of water may operate through effects on some mechanism not yet disclosed; and (3) the causes of these changes in resistance may be found in the interlocked influences of organs of internal secretion affecting not only sugar metabolism, but also the unknown means by which the body cells resist bacterial invasion and the deleterious effects of bacterial products.

Blood Sugar in Experimental Diabetes*

Harold E. Himwich
Albany

I greatly appreciate the honor of being invited by Dr. Mosenthal to participate in the exchange of ideas on the subject of blood sugar in diabetes. Dr. Bayne-Jones has clarified the relationship of blood sugar to infections. My topic is blood sugar in experimental diabetes. There are two points of view in the treatment of diabetes. The first one calls for the maintenance of a normal blood sugar with values between 100 and 140 mgm. per cent. The second point of view permits and even entertains a preference for higher levels of blood sugar as long as they are not accompanied by marked glycosuria and by ketosis. Tonight I shall review the evidence obtained from experimental studies of diabetes and also present new data in order to evaluate these two opposing conceptions of the management of diabetes.

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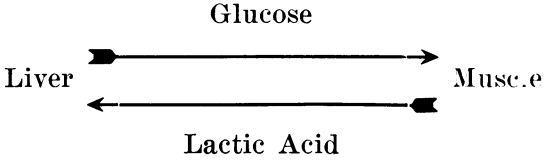
* From the Department of Physiology and Pharmacology, Albany Medical College, Albany, N. Y.

It is interesting to recall that the liver is the source of the blood sugar. After ingestion of carbohydrates, blood sugar rises, a result of the exogenous carbohydrates, but in the post-absorptive state, the level of the blood sugar is

FIGURE I.



maintained by the breakdown of liver glycogen. With Doctors Chambers, Koskoff and Nahum,[5] we were able to show that in diabetes, as in normal conditions, the mechanism which maintains blood sugar links muscle and liver in an intimate manner. Glycogen is not retained by the liver but breaks down to glucose, giving rise to the characteristic hyperglycemia of diabetes. This glucose circulates in the blood, is absorbed by all the organs, and particularly so by the large masses of muscle tissue. In muscle, glucose is synthesized to glycogen. However, this glycogen is not locked in the muscles. With muscular activity, it gives rise to lactic acid, and it should be noted, not to glucose. Apparently the ability of muscle to form lactic acid may be impaired but does not cease with the development of the diabetic state. Lactic acid then diffuses out of muscle to blood. This permits the liver to absorb lactic acid from the blood and resynthesize it to form glycogen. In this manner, the hyperglycemic level of the blood is maintained in the post-digestive state during diabetes.

We must examine next the factors which regulate the level of the blood sugar. In this regard the endocrine glands are determining influences. Though inability to oxidize glucose necessarily causes an increase of blood sugar, it should be remembered that the concentration of the glucose of the blood is responsive not only to the secretions of the islands of Langerhans but also to those of other endocrine glands. The anterior pituitary, the adrenal, and the thyroid glands may act either synergistically or sepa-

rately to raise blood sugar. This they do by mobilizing liver glycogen and not necessarily by inhibiting the oxidation of glucose. Acromegaly in 40 per cent of all cases, may be accompanied intermittently by signs of diabetes including an increased blood sugar and a ketosis.[8] The secretions of the anterior pituitary gland influence both carbohydrate and fat metabolism by liberating liver glycogen and stimulating fat oxidation. It is, therefore, incorrect to regard a high blood sugar and a ketosis as due necessarily to exhaustion of the islands of Langerhans. In patients with acromegaly the administration of insulin may be singularly ineffective. This action is explained by Houssay and Biasotti's[8] conclusion that the anterior pituitary gland contains a hormone which inhibits the oxidation of carbohydrate. However, it should be noted that Chambers, Sweet and Chandler[3] believe that the anterior pituitary does not inhibit the oxidation of carbohydrate.

The hormone of the medulla of the adrenal gland, like that of the anterior pituitary gland, affects liver glycogen. Cope and Marks[4] have demonstrated that the secretions of the anterior pituitary and adrenal medulla act synergistically to deplete the liver of its glycogen. In a like manner, overactivity of the thyroid gland tends to diminish liver glycogen and therefore raise blood sugar without, however, inhibiting the oxidation of carbohydrate. Thus the concentration of glucose in the blood is not necessarily a gauge of the function of the islands of Langerhans but is a resultant of the interactions of various endocrine glands. The level of the blood sugar cannot, therefore, be regarded as the sole criterion for the body to oxidize carbohydrate and thus should not be used exclusively as an index for the amount of insulin necessary for the control of diabetes.

Later we hope to show that in contrast with blood sugar, urinary glucose may be of greater significance in determining the dosage of insulin. But first we must consider the effects of a heightened level of sugar in the blood on the metabolism of carbohydrate.

An increased concentration of blood sugar serves as a stimulus to carbohydrate metabolism. In response to the

rise of blood sugar following the ingestion of carbohydrate, glycogen is stored in liver and muscle while the oxidation of glucose is accelerated. In partial diabetes where the carbohydrate mechanisms of the body are impaired but still function to some degree, it is probable that a high level of blood sugar acts as it does in the normal individual to increase the metabolism of carbohydrate. Indeed, even in the diabetes following total pancreatectomy a high level of blood sugar aids in the storage of carbohydrate. Major and Mann[10] found that intravenous injection of glucose increased the deposition of glycogen in liver and muscle of depancreatized dogs. On the other hand, removal of the liver is followed by a gradual and continuous decline of blood sugar. Mann and Magath[11] first studied dogs with pancreas intact and therefore unimpaired ability to oxidize carbohydrate. After hepatectomy, hypoglycemia always developed in these animals. With the removal of the liver, the cycle between muscle and liver was interrupted and the blood sugar decreased. When the glucose of the blood fell to the low level of 20 mgm. per cent hypoglycemic convulsions occurred. These convulsions are, therefore, the response of the body to lack of carbohydrate. Mann and Magath[11] also removed the liver of dogs that had been depancreatized three or four days previously. These dogs initially had the high blood sugar characteristic of diabetes. Following hepatectomy of the depancreatized dogs, glucose was utilized for there was a progressive decrease of blood sugar just as in the non-diabetic animals. However, in the depancreatized animals convulsions, indistinguishable from hypoglycemic paroxysms, occurred at levels of blood sugar higher than 100 mgm. per cent or even 200 mgm. per cent. Thus in diabetes, a decline of blood sugar, even though to values still well above normal, is followed nevertheless by symptoms similar to those of hypoglycemia in the animal with pancreas intact. These data have been interpreted by Lesser[9] to indicate that a concentration of blood sugar greater than normal is necessary for the utilization of carbohydrate during diabetes. With impairment of carbohydrate oxidation, an increased

concentration of blood sugar is therefore compensatory, insuring a better utilization of carbohydrate. The improvement in the metabolism of carbohydrate must have an immediate effect on the utilization of fat, for an increased oxidation of glucose necessarily causes a better combustion of fat. The conception that high blood sugar aids the utilization of carbohydrate is, therefore, of utmost importance in the management of diabetes. It indicates the advantage of maintaining high levels of blood sugar. This applies especially to patients with raised renal thresholds for glucose.

Though a high blood sugar is beneficial, the ingestion of carbohydrate in quantities in excess of the oxidative capacities of the body has an adverse effect. Before insulin was discovered, it was a common experience to observe failure of the insular mechanisms as a result of the ingestion of carbohydrate in quantities greater than could be metabolized by the patient. The overtaxed oxidations became completely, if temporarily, exhausted. Today, however, such consequences are no longer to be feared for the administration of adequate amounts of insulin spares the endogenous mechanisms from an excessive load. Moreover, a higher blood sugar level is not necessarily a strain on the ability to oxidize carbohydrate. Mosenthal[12] has stressed that a high blood sugar may be maintained for long periods with no deleterious effects in patients with diabetes. Indeed, many people with no apparent defect in the oxidation of carbohydrate exhibit levels of blood sugar well above the usual average values. This is in accord with our previous conclusion that a high level of blood sugar is not necessarily a sign of impairment of the functions of the islands of Langerhans but may indicate instead a mobilization of liver glycogen due to overactivity of other endocrine glands.

If an increased blood sugar does not necessarily injure, and may, in fact, aid the metabolism of carbohydrate, where then, does the chief disadvantage of high blood sugar lie? At present, the evidence indicates that a most serious danger in diabetes is dehydration, which may lead to collapse. Dehydration, moreover, is an element of diabetic

coma. The inception of dehydration lies in the production of the ketone acids. With the impairment of carbohydrate metabolism, additional fat must be oxidized if life is to be maintained. However, the diminished ability to oxidize carbohydrate makes the complete combustion of fat impossible. As a result, acetone substances accumulate. Therefore, a specific acidosis, a ketosis, supervenes. This is the characteristic acidosis or ketosis of diabetes. One of the chief compensatory mechanisms to overcome this ketosis resides in the function of the kidney to produce ammonia for the formation of ammonia salts. These ammonia salts of the acetone substances are eliminated in the urine, and in this manner the ketosis is diminished. However, in severe diabetes, ketone acids accumulate more rapidly than the kidney can form ammonia. All the ketone substances cannot, therefore, be eliminated as ammonia salts. For this reason, the sodium of the blood must be utilized for this process. Thus sodium salts of the ketone acids are also excreted and appear in the urine. When sodium leaves the body, it has an entirely different effect than has ammonia, for sodium is a constituent of the body fluids. The loss of sodium would render the body fluids hypotonic, that is, too dilute, if water were not excreted with the sodium. As a result of the diminished sodium content of the blood, water is eliminated and the dangerous dehydration of diabetes supervenes. This conception, presented by Peters[13] describes one of the two mechanisms of dehydration in diabetes.

TABLE I.

A MECHANISM OF DIABETIC DEHYDRATION

1. Ketonuria
2. Sodium Salts
3. Water

As you will note in the table, the first step in the process of dehydration consists of the elimination of ketone substances. The second involves the excretion of sodium as an aid in the elimination of the acetone substances, and finally the loss of water follows that of the sodium salts.

In 1933 Atchley, Loeb, and their co-workers[2] suggested a second potent mechanism in the causation of diabetic dehydration. These investigators studied two patients with severe diabetes. One required approximately 85 units of insulin daily, and the other about 75 units of insulin to maintain the urine free of sugar. In both these patients, insulin injections were stopped for short experimental periods. With both patients a glycosuria, a polyuria, and a dehydration ensued. Despite the fact that in both patients organic acids of the urine increased and in one of these cases the ketonuria was marked, Atchley, Loeb, and their co-workers[2] were able to dissociate the dehydration secondary to glycosuria from that produced by the acidosis and therefore came to the conclusion that glycosuria, of itself, may be a cause of dehydration. That glycosuria can produce dehydration has been demonstrated in previous work of our laboratory. In a paper presented from this platform during the Graduate Fortnight in 1933, [6, 7] we were able to show that concomitant with the loss of glucose in the urine, dehydration occurred. Acute depletion of the body fluids resulted in the development of fever; diabetic hyperpyrexia. In studies now being made in our laboratory at Albany, we are attempting to examine the mechanism of dehydration when there is no ketosis to initiate the loss of the body fluids. We are employing the partially depancreatized preparation used so effectively by Frederick M. Allen.[1] Our animals weigh from 7 to 15 kilos and usually all but one or two grams of their pancreas are removed aseptically. In many respects this preparation resembles that of a human being with diabetes, for not only are some of the external secretions, the digestive enzymes, of the pancreas retained but also a portion of the internal secretions and therefore partial ability to oxidize carbohydrate. Examinations of the blood sugar disclosed, moreover, that the oral administration of one gram of glucose per kilo of body weight produced the typical heightened and prolonged glucose tolerance curve of severe diabetes. Our preliminary observations revealed a close correlation between the amount of glucose excreted in the urine and the total bases, especially

the sodium, of the urine. When sugar was excreted, water was also eliminated and with the water, salts, chiefly, sodium chloride. We next stabilized our animals much in the same fashion as patients with diabetes. They were given carbohydrate, fat and protein in amounts sufficient to maintain caloric equilibrium and insulin in doses adequate to prevent glycosuria. Salt was added to the diet in an attempt to prevent rapid depletion of the sodium reserves. Due to the diabetic condition of these animals, the post-absorptive level of the blood sugar was high, up to 300 mgm. and more. Nevertheless, with the aid of insulin, daily loss of sugar in the urine was not significant. Despite a high level of blood sugar with no glycosuria, there was no polyuria, and no dehydration. High blood sugar of itself produces no dehydration.

This fact is particularly important in human diabetes and especially so in cases of some duration in which the renal threshold rises as the disease continues. These observations leave no doubt that a high blood sugar in patients with diabetes will produce no dehydration when unattended by glycosuria. The next step was to study the effect of glycosuria. To do this we increased the glucose content of the food of these animals. No other change was made in the diet and the dosage of insulin was kept unaltered. Thus, unlike the previous experiments of Atchley, Loeb, and their co-workers, the present observations involved no decreased oxidation of carbohydrate and therefore no accumulation of acid substances. Thus, the only direct effect of this change in the diet was the production of glycosuria. Nevertheless, the glycosuria was accompanied by a polyuria. Though the kidney may concentrate glucose to 10 per cent or more, additional water must also be excreted by the kidney. The glycosuria forces an increased renal excretion of fluids.

In the table are presented the data of one of our animals. They represent the results of three control days just before the ingestion of increased amount of glucose and the analyses of the last three days of an eight day period of glycosuria without ketonuria. The augmented ingestion of

glucose produces a glycosuria. Associated with an increase of glucose is that of the volume of the urine. The polyuria increases the quantities of base or salts of the urine. Apparently water is eliminated with salt. Therefore, there is a direct relationship between the glucose, the urinary volume and the salts excreted. They all increase together. As you can see in the last column the intake of water is augmented. This also must be attributed to the glycosuria. The water supplied to our animals was unlimited. The salt content of the diet was, however, kept constant. With increasing urinary volume, the output of salt or base finally exceeded the intake. As a result, the sodium of the body was depleted. With the loss of sodium and water, dehydration developed. The depletion of body fluids over the period of eight days is evidenced by the loss of weight.

TABLE II.

EFFECT OF GLYCOSURIA WITHOUT KETONURIA ON URINE

Date Jan.	*Glucose Grams*	*Volume CC.*	*Base M.E.*	*Water Intake CC.*
5	0	156	21.0	565
6	0	210	38.6	330
7	0	129	23.7	360
13	44.7	630	65.7	1000
14	77.5	1360	73.0	1400
15	73.2	1200	60.3	1560

TABLE III.

EFFECT OF GLYCOSURIA

Eight Days

		Blood	
	Weight Kilos	*Serum Protein Per Cent*	*Oxygen Capacity Vol. Per Cent*
Control	7.20	6.38	17.60
Dehydration	7.00	7.07	18.94

This decrease of weight correlates with the greater volume of the urine. The diminution of the fluids of the body may also be seen by the increased serum protein and the raised oxygen capacity of the blood, results of dehydration.

TABLE IV.

MECHANISMS OF DIABETIC DEHYDRATION

1. Ketonuria	1. Glycosuria
2. Sodium Salts	2. Water
3. Water	3. Sodium Salts

Here then is a second mechanism of dehydration. As presented in the table, it is initiated by the glycosuria which increases the excretion of water, thus producing a polyuria and finally a loss of salt. In contrast to the mechanism previously described in which the inception of the dehydration was caused by a ketonuria, the loss of sodium preceding that of water, in the present experiments by avoiding ketonuria, it has been possible to demonstrate that the loss of water may be the cause of the depreciation of the sodium reserves of the body.

If this is so, then the administration of added amounts of salt in the diet should prevent dehydration. We gave our animals, depleted of salt and water, an additional 10 grams of salt daily for two days, and despite the continued glycosuria observed in these dehydrated animals, a subsequent dilution of the blood and a gain of weight due to restoration of the body fluids. Water was retained and the salt deficit was made up. Even though dehydration is conditioned by loss of salt, it must be remembered that the cause of the depreciation of the salt of the body is the presence of excessive amounts of sugar in the urine. These observations suggest, therefore, that in the management of diabetes, the examination of urinary sugar is more significant than that of blood sugar. As long as the glycosuria is not excessive, there is no fear of dehydration. A slight glycosuria is, however, only of secondary importance. The loss of a relatively small amount of energy containing substances in the urine is not serious.

The review of the literature and the new evidence leads to the following four conclusions. (1) The level of the blood sugar is a resultant of the activity of various endocrine glands. It is, therefore, not necessarily an index of impaired ability of the islands of Langerhans but may indicate instead hyperfunction of the adrenal, the thyroid, and particularly of the anterior pituitary glands. (2) During diabetes as in the normal, an increased concentration of blood sugar serves as a stimulus to carbohydrate metabolism and therefore is not to be combatted unless accompanied by a definite glycosuria. (3) Dehydration may be a result of glycosuria. The development of a marked glycosuria should, therefore, never be permitted to continue even for short periods. (4) And finally, as a result of the three previous conclusions, it follows that the glucose content of the urine rather than that of the blood should be taken as the criterion of the amount of insulin indicated in diabetes mellitus.

BIBLIOGRAPHY

1. Allen, F. M. Experimental Studies in Diabetes. Series I. Production and Control of Diabetes in the Dog. I. Gross Anatomic Relations of the Pancreas and Diabetes. *J. Exp. Med.*, 1920, *31:* 363-379.
2. Atchley, D. W., R. F. Loeb, D. W. Richards, E. M. Benedict, and M. E. Driscoll. On Diabetic Acidosis; a detailed study of electrolyte balance following the withdrawal and re-establishment of insulin therapy. *J. Clin. Invest.*, 1933, *12:* 297-326.
3. Chambers, W. H., J. E. Sweet and J. P. Chandler. Carbohydrate Metabolism in the Hypophysectomized Dog. *Am. J. Physiol.*, 1935, *113:* 26-27.
4. Cope, O., and H. P. Marks. Further Experiments on the Relation of the Pituitary Gland to the Action of Insulin and Adrenaline. *J. Physiol.*, 1935, *83:* 171-176.
5. Himwich, H. E., W. H. Chambers, Y. D. Koskoff, and L. H. Nahum. Studies in Carbohydrate Metabolism. II. Glucose-lactic acid cycle in diabetes. *J. Biol. Chem.*, 1931, *90:* 417-426.
6. Himwich, H. E. The Metabolism of Fever with Special Reference to Diabetic Hyperpyrexia. *Bull. N. Y. Acad. Med.*, 1934, *10:* 16-36.
7. Himwich, H. E., J. F. Fazikas, L. H. Nahum, D. Du Bois, L. Greenburg, and A. Gilman. Diabetic Hyperpyrexia. *Am. J. Physiol.*, 1934, *110:* 19-27.

8. Houssay, B. A. and A. Biasotti. The Hypophysis, Carbohydrate Metabolism and Diabetes. *Endocrinology,* 1931, *15:* 511-523.

9. Lesser, E. J. Die innere Sekretion des Pankreas. Jena, 1924.

10. Major, S. G. and F. C. Mann. Formation of Glycogen following Pancreatectomy. *Am. J. Physiol.,* 1932, *102:* 409-421.

11. Mann, F. C. and T. B. Magath. Studies on the Physiology of the Liver. II. The effect of the removal of the liver on the blood sugar level. *Arch. Int. Med.,* 1922, *30:* 73. IV. Effect of total removal of the liver after pancreatectomy on the blood sugar level. *Arch. Int. Med.,* 1923, *31:* 797.

12. Mosenthal, H. O. Hyperglycemia: Evaluation in treatment of diabetes mellitus. *J. A. M. A.,* 1935, *105:* 484-487.

13. Peters, J. P. Acid-Base Equilibrium and Salt and Water Exchange. *Yale J. Biol. Med.,* 1930, *2:* 183-221.

Blood Sugar in Diabetes Mellitus*

Edward Tolstoi

New York

The blood sugar is an excellent and useful criterion of the behavior of carbohydrate metabolism. Regulated by normal physiological processes, the sugar of the blood has a constancy within definite limits, and in its behavior like other biological constants it tends to return to its original level when the factor for its alteration is corrected. After the complex carbohydrates are simplified by the digestive enzymes in the gastro-intestinal tract, they are carried as glucose by the portal vein to the liver where a molecular rearrangement takes place and glycogen is formed. This biochemical process is not always in one direction. It is reversible, and it is inferred that the liver can also supply the blood with glucose from the glycogen it has stored. It is obvious, therefore, that the liver plays a most significant role in the metabolism of carbohydrates. It is the carbohydrate storehouse, storing the sugars in the form of glycogen and making excellent use of its savings when the organism is in want of sugars and cannot for various reasons

* From the New York Hospital and the Department of Medicine, Cornell University Medical College.